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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,726	10/01/2002	Shun-ichiro Matsumoto	6235-62514	6930

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EXAMINER	
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ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,726	MATSUMOTO ET AL.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *7-14,16,17 and 22-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,15 and 18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/1/04,12/19/03*. 4/11/02, 12/28/01
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Amendments filed 10/1/02 and 1/23/06 have been entered.

2. IDS file 12/28/04, 10/1/04, 12/19/03 and 6/17/02 have been considered.

Election/Restriction

3. Applicant's election with traverse of Group I, (claims 1-4, 6, 15, 18-20 and 25, SEQ ID NOS:20 and 25) on 1/23/06 is acknowledged. The traversal is on the ground(s) that the inventions of Groups I-II are not independent or distinct due to amendment of claim 1. Applicants request the polypeptide of Group II be combined with the polynucleotide of Group I. Applicant's argument is found persuasive. Group II (claims 5 and 21) will be combined with group I and examined. Claims 7-14, 16-17, 22-27 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The requirement is still deemed proper and is therefore made FINAL.

4. **Objections**

The disclosure is objected to because of the following informalities:

A. The specification contains numerous incomplete sentences, which contain "(# # # # # #)" e.g. page 57. The symbols appear inappropriately in the sentences and it is not clear what they represent.

Appropriate correction is required throughout the specification.

B. The specification should be reviewed for improper recitation of hyperlinks. All such recitations should be deleted or amended such that the hyperlinks are rendered inactive. See MPEP 608.01.

C. The claims are objected to because of the following informalities:

Claim 15 contains non-elected invention (SEQ ID NO:5-8 and 23-26). Non-elected inventions must be removed from claim 15.

5. ***Sequence Rules Compliance***

This application fails to comply with the sequence rules, 37 CFR 1.821-1.825. Nucleotide and polypeptide sequences must be identified with the corresponding SEQ ID NO. Title 37, Code of Federal Regulations, Section 1.821 states reference must be made to the sequence by use of the assigned identifier, the identifier being SEQ ID NO. Polynucleotide sequences in Figures 1-9, 11-12, 14, 16, 18-19, 21, 23-25, 27, 29-30 and 32-34 must be identified by their corresponding SEQ ID NO:. Further there are numerous sequences in the specification that are not identified by SEQ ID NO:, e.g. pages 26-28. The whole specification must be compliant with the Sequence rules. Compliance with sequence rules is required.

Priority

6. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. [1] as follows:

Applicant is advised of possible benefits under 35 U.S.C. 119(a)-(d), wherein an application for patent filed in the United States may be entitled to the benefit of the filing date of a prior application filed in a foreign country.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 5, 15 and 21 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 15 recites a polynucleotide but do not recite that it is isolated or purified. Claims 5 and 21 recite a protein or peptide but do not recite that they are isolated or purified. The claims as currently recited encompass these naturally occurring compounds. Therefore, the compounds as claimed are a product that occurs in nature and does not show the hand of man, and as such is non-statutory subject matter. It is suggested that the claims be amended to recite "an isolated and purified" polynucleotide and "an isolated and purified" protein to overcome this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-6, 15, 18-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 is indefinite because stringent conditions of hybridization are not specified. It is not clear what are the "stringent conditions". The metes and bounds of the group of sequences that would meet the limitations of the claim depend upon the precise conditions under which hybridizations were performed including wash conditions. Since the hybridization and wash conditions dictate which nucleic acid sequences remain specifically bound to the claimed polynucleotide the metes and bounds of the claim cannot be determined without the disclosure of said conditions.

Claim 6 is indefinite because the method steps do not achieve the goal of producing a protein or peptide encoded by the DNA of claim 1. The method steps are directed at "recovering an expressed protein or peptide", there is no indication that the recovered expressed protein is encoded by the DNA of claim The "an expressed protein or peptide" can be any protein or peptide. It is

suggested to overcome the rejection the claim be amended to recite, " recovering the protein or peptide encoded by the DNA of claim 1".

Claim 2 is indefinite because it is not clear when a peptide is considered a partial peptide so as to allow the metes and bounds of the claim to be determined. Examiner has interpreted peptide as being a natural or synthetic compound as containing two or more amino acids linked by the carboxyl group of one amino acid and the amino group of another. Therefore a partial peptide is considered by the examiner to mean any part of a peptide which is less than two amino acid, said part can be an atom or even an ion. It is not clear how the DNA can encode an ion.

Claim 20 recites the limitation "the vector of claim 4" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 3-5, 15, 18-19 and 21 are rejected for depending upon an indefinite base (or intermediate) claim and fail to resolve the issues raised above.

Claim Rejections - 35 USC 101 and 35 USC 112, 1st paragraph

The following is a quotation of 35 U.S.C. 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-6, 15, 18-21 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

A specific utility is a utility that is specific to the subject matter claimed, as opposed to a general utility that would be applicable to the broad class of the invention. A "substantial utility" is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. A "well established utility" is a utility that is well known, immediately apparent, or implied by the specifications disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. A well established utility must also be specific and substantial as well as credible.

Based on the record, there is not a "well established utility" for the claimed invention. Applicant has asserted utilities for the specifically claimed invention of claims 1-6, 15, 18-21. Claims are drawn to DNA (SEQ ID NO:25 or variants thereof) encoding the guanosine triphospahte-binding (GPCR) protein GPRv71 of SEQ ID NO:20 or variants thereof, vector comprising said DNA, transformant

comprising the DNA and method of producing the protein. GPRv71 polypeptide (seven transmembrane domains) is disclosed to have the highest homology (45%) to P2Y3 receptor and is classified in the rhodopsin family of GPCR by the results of HMMPfam search. GPRv71 polypeptide concluded to be a GPCR based on homology to P2Y3 receptor (specification, page 35). The specification, page 23, discloses, "The expression level of GPRv71 decreased in the colon and kidney, and was undetectable in the liver, after cirrhosis. In Alzheimer's disease, the expression level decreased in the frontal lobe. Accordingly, when the expression of GPRv71 is detected in the colon or kidney at a lower level than the normal level, the subject is suspected of colon cancer or kidney cancer. Further, when the expression of GPRv71 is detected in the liver at a lower level than the normal level, the subject is suspected of cirrhosis. Further, when the expression of GPRv7l is detected in the frontal lobe at a lower level than the normal level, the subject is suspected of Alzheimer's disease".

The specification, on page 23, pertaining to expression of GPRv71 does not disclose: the level of expression of GPRv71 in the liver before cirrhosis, the assay used for detection of GPRv71, the probe used in the assay, the sensitivity of the assay, the number of samples tested, whether the controls were from liver or some other tissue, if the sample was taken from a patient on any medication, if the tissue was human, if the sample was from a dead or live animal. It is not even clear from the specification if GPRv71 is expressed in the liver before cirrhosis. It is also not clear if the determination of "level of expression" measured the protein levels or merely mRNA in the assay. All these limitations

will determine if GPRv71 or more specifically the absence of GPRv71 in the liver can be used a marker for the liver cirrhosis. For example, if only one sample is tested there are many reasons apart from liver cirrhosis that may account for the absence of expression. One of the reasons being the expressed GPRv71 could contain a mutation that results in a truncated variant and the probe used for detection does not recognize polynucleotide. Vanti et al (Vanti et al., Genomics 82, 531-536, 2003) discloses that null mutations can arise in a GPCR that renders it truncated and non-functional). Therefore, in the case of the Vanti variant the wrong probe would not detect anything. Also Ta-Tung (Ta-Tung et al, Gene, Vol. 278, pages 41-45, 2001) discloses the assay and tissue used is very important in determing the information gleaned. Ta-Tung discloses (page 49, column 2) that although PSGR (a GPCR) RNA could not be detected by northern analysis in total RNA from whole brain tissue, RT-PCR analysis of five human brain tissue analyses of five regions did reveal the presence of PSGR mRNA specifically in the olfactory epithelium and medulla oblongata (Fig. 3). Another reason that may account for the absence of expression, the patient could be on medication that prevents the expression of GPRv71. The sample could also be from a tissue sample where the mRNA encoding GPRv71 has been degraded by enzymes due to storage. The specification states, "Further, when the expression of GPRv71 is detected in the liver at a lower level than the normal level, the subject is suspected of cirrhosis". There is no indication at what level of detection GPRv71 polynucleotide or protein in the liver is the threshold for determining liver cirrhosis. Based on the disclosure there is insufficient information provided on

which to base a utility of using GPRv71 as a marker for liver cirrhosis. Similarly, there is a lack of experimental detail and results for use of GPRv71 as a marker for colon or kidney cancer, or diagnosis of Alzheimer's disease.

Applicant has classified the GPCR of SEQ ID NO:2 into the superfamily of GPCRs. The specification discloses the GPCR of SEQ ID NO:20 can be used to identify test compounds which bind said receptor. The GPCR of SEQ ID NO:20 is disclosed is to be potentially involved in a variety of unrelated disease states. It noted that neither the specific activity of GPCR of SEQ ID NO:20 or the specific treatable disease associated with the GPCR of SEQ ID NO:20 is disclosed. There is no disclosure of the specific activity of claimed GPCR. Ligands that bind or activate said GPCR are disclosed. In light of the specification the skilled artisan cannot come to any conclusions as to the function of the GPRv71 polypeptide G protein-coupled receptor of SEQ ID NO:20. The utility of claimed GPRv71 polypeptide cannot be implicated solely from homology to the proteins known in the art because the art does not provide teaching stating that all protein disclosed have the same activity, same effects, the same ligands and are involved in the same disease states (discussed later). In light of the specification and art the skilled artisan cannot come to any conclusions as to the function of polynucleotide or its encoded protein in instant invention. There is no disclosure provided within the instant specification on what specific function the protein of SEQ ID NO:20 possesses, or how to use compounds that bind said protein. No disease states are disclosed that are directly related to GPRv71 polypeptide dysfunction.

The specification fails to disclose, what disease is associated with claimed receptor dysfunction or what drugs affect a specific claimed receptor function. The GPCR may have utility in the future, when it has been further characterized (e.g. its dysfunction or function correlated with a disease state) and its ligand characterized. The inclusion in the family of G protein coupled receptors (GPCR) does not constitute either a specific and substantial asserted utility or a well-established utility for that particular GPCR or protein. This is analogous to all proteins or GPCRs can be used as protein markers on a gel.

Specification discloses claimed receptors are useful in screening but the specification does not disclose what claimed receptor specifically regulates and what specific disease the receptor is a target for. What would be the use of using the claimed receptor on a panel for drug screening? The receptor has no known ligand or known function. How would one use the compounds that interacted with said orphan receptors? The specification provides a diverse list of disease states that may be involved in receptor dysfunction. It is unpredictable what ligands will bind to orphan receptors, and further the functional effects of ligand binding may remain uncertain even after extensive experimentation. What is the utility for a ligand, in many cases with no known function, that binds to a receptor of no known function? The ordinary artisan can only speculate on the utility for the ligand and receptor. A utility to orphan receptor cannot be assigned without knowledge of what disease is associated with claimed receptor dysfunction or what drugs/ligands affect a specific claimed receptor function. Members of a sub-family of G-protein-coupled receptors are also highly divergent in their

effects, as highlighted by Murdoch et al (Blood, Volume 95, No.10, pages 3032-3043, 2000), in the discussion of cytokine G-protein-coupled receptors. The utility of claimed receptor cannot be implicated solely from homology to known G-protein coupled receptors or their protein domains because the art does not provide teaching stating that all members of family of G-protein coupled receptors must have the same effects, the same ligands and be involved in the same disease states, the art discloses evidence to the contrary. The specification has not even used protein domains/homology to predict the activity of the protein. Murdoch discloses the superfamily of G-protein-coupled receptors are highly divergent in their effects and include receptors for hormones, neurotransmitters, paracrine substances, inflammatory mediators, certain proteinases, taste and odorant molecules, and even photons and calcium ions. Further, the G-protein that interacts with the claimed orphan receptor and is required for the signal transduction activity is unknown. Watson (The G-Protein Linked receptor Facts Book, pages 2-6 and 223-230, 1994) states "it has therefore not been possible to identify consensus amino acid sequences that confer G-protein specificity, and thus G-protein interactions cannot be predicted from the primary amino acid sequence". Therefore the disclosure of Watson predicts, using the primary structure of the G-protein coupled receptor the skilled artisan cannot predict its associated G-protein or its ligand. G-protein coupled receptors are highly specialized and ligand specific proteins. The superfamily of seven transmembrane domain G-protein coupled receptors are specialized proteins designed for chemical recognition of ligands and subsequent

transduction of information encoded in those ligands to the machinery of the cell, and the G-protein coupled receptors interact with alkaloids, biogenic amines, peptides, glycoprotein hormones, light and odorants (Terry Kenakin, Pharmacological Reviews, Vol. 48, No.3, pages 413-462), see page 413. Kenakin also states, "To achieve information transfer, the ability to bind ligands to a recognition domain and allosterically transmit the presence of that ligand to an intracellular domain appears to be a specialized feature of 7TM receptors. The very properties that define receptors as such also impart unique protein behaviors to receptors, and these behaviors, in turn, affect drug activity", page 414, column 1, second paragraph. Bork (Nature Genetics, Vol. 18, pages 313-318, 1998) provide a review article disclosing the problems of using homology detection methods to assigning function to related members of a family. Bork discloses: a) "While current homology detection methods can cope with data flow, the identification, verification and annotation of functional features need to be drastically improved", page 313, column 1, Abstract, b) there are two bottle necks that need to be overcome en route to efficient functional predictions from protein sequences, i.e., "First, there is the lack of a widely accepted, robust and continuously updated suite of sequence analysis methods integrated into coherent and efficient prediction system. Second, there is considerable 'noise' in the presentation of experimental information, leading to insufficient or erroneous function assignment in sequence databases", page 313, column 1, third paragraph, c) "In-depth analysis of protein sequences often results in functional predictions not attained in the original studies", page 313, column 2, last

paragraph, d) "However, more often than not, it is clear that the cellular role of the protein in question differs from that of the detected homologue(s) and there is currently no automatic means to establish how much functional information can be legitimately transferred by analogy from homologue to the query", page 315, column 2, last paragraph, e) pertaining to predictions of protein function, "Do not simply transfer functional information from the best hit. The best hit is frequently hypothetical or poorly annotated; other hits with similar or even lower scores may be more informative; even the best hit may have a different function", while "many proteins are multi functional; assignment of a single function, which is still common in genome projects, results in loss of information and outright errors" and "It is typical that the general function of a protein can be identified easily but the prediction of substrate specificity is unwarranted; for example, many permeases of different specificity show approximately the same level of similarity to each other", page 316. Karp (Bioinformatics, Vol. 14, No.9, pages 753-754, 1998) has disclosed the problems of using functional prediction based on homology analysis. Karp states, a) "Although we know the accuracy with which sequence homologs can be determined, we know little about the accuracy of the overall process of assigning function by homology, page 753, column 2, second paragraph, b) "We have more faith in the correctness of those sequences whose functions we determined experimentally, rather than through computational means, page 753, column 2, last paragraph, c) "research is required to estimate the error rate of functional annotation by different methods of computational sequence analysis", page 754, column 2, last paragraph. Bork (Current Opinion

in Structural Biology, Vol. 8, pages 331-332, 1998), discusses the problems with deriving biological knowledge from genomic sequences and states, "structural similarity does not lead to iron-clad functional predictions" page 331, column 2 last paragraph, "Structural similarity does not necessarily mean a common evolutionary origin" page 332, column 1, second paragraph, and "Today, what we predict from sequences is at best fragmentary and qualitative", page 332, column 2, second paragraph.

Civelli et al (Civelli et al, Pharmacology and Therapeutics, November 8, pages 1-8, 2005) discloses that all 7 transmembrane receptors are not GPCRs (page 2, column 1). GPCRs are activated by a plethora of transmitters and have a broad spectrum of interactions. The role of GPCRs in various tissues may be different although the second messengers that result from its initial activation are probably the same. Most GPCRs started as orphan receptors and the discovery of new members found by homology screening suffers from one obvious problem, the receptors found lack their pharmacological identities, their natural ligands (gage 2). The pursuit to unravel their identities has led to fishing expeditions. The number of orphan GPCRs has steadily increased and at this time the GPCRs outnumber the known potential ligands. Researchers utilize orphan receptors as baits to isolate their natural ligands, which is meant to identify novel transmitters (page 3). Civelli also discloses the discovery of the natural ligand is no easy task, and specifically states, "GPCRs have been depolarized at a rate of 7-8 per year from 1999 until 2004. This was mostly the result of large-scale random screening of practically all molecules known to exist

in cell", (page 4, column 2). There is no rule for predicting the affinity constant of a natural ligand at a particular receptor. The level of receptor expression in a transfected cell can affect ligand potency and is subject to artifacts. Belonging to a family of GPCRs does not insure that all members will bind the same ligand or have the same effects. The recently discovered Mas-related GPCRs, orphan receptors, bind a variety of structurally divers transmitters (ligands), Rfamide peptides for some mouse Mrgs and cortistatin for two human Mrgs, adenine for rat Mrg and beta-alanine for an Mrg found in human, rat and mouse (column 2, page 5). The matched transmitters are specific to particular Mrgs and activate them efficiently. By the mid-1990s approximately 90 transmitters were known, since then, a dozen new transmitters have been found and it is expected that the remaining 120 orphan GPCRs will lead to the discovery of at least 50 more transmitters (page 6, column 1). There is no doubt that orphan GPCRs are used as potential drug targets but there is no marketed drug directed at any of the ones that have been depolarized since 1995 (page 6, column 1). Many targets even when recognized of therapeutic interest have showed no value for drug screening (table 2).

Hancock (Hancock, A.A., Biochemical Pharmacology, Vol. 71, pages 1103-1113, 2006) discloses although histamine H3 receptor (GPCR) was identified pharmacologically in 1993, and despite widespread pharmaceutical interest in the target, no compound interacting specifically with this site has undergone successful clinical examination to develop the necessary proof-of-concept data. The pharmacological effects of known H3 ligands are complex

and diverse, since these agents may act both as agonists and antagonists in different systems. Moreover, other compounds show inverse agonism in some models but neutral antagonistic activity in others (see abstract).

Feng et al (Feng et al., Kidney Research, May, Vol. 67, Issue 5, pages 1731-1738, 2005) discloses the heterogeneity for a GPCR AT2 receptor in both ligand binding and induction of arachidonic acid release. The AT2 receptor exhibits distinct biochemical and biological properties compared to its highly homologous orthologues (91% homologous in overall amino acid sequence) of rat, mouse and human. The reducing agent DTT inactivates the rabbit othhologue but potentates the others in ligand binding. Rabbit AT2 receptor but not the other orthologues, induces arachidonic acid release in various cell systems when stimulated with Ang II and CGP42112A, the peptide antagonist. Mutagenesis studies and sequence analysis further indicate that residues His106, ASP188 and Thr393 are responsible for DTT inactivation and residues Val209 and Val249 are partially responsible for arcchidonic acid release (see Abstract)

Marchese et al (Marchese et al., TIPS, Vol. 20, pages 370-375, September 1999) discloses the search for novel GPCR genes (cloning by low stringency hybridization to cDNA/genomic DNA libraries) has far outpaced the identification of novel endogenous ligands, more than 80 orphan GPCRs are awaiting a ligand. Many orphan GPCRs are found to be similar to known GPCRs. Where the identity reaches the threshold of approximately 45% it is likely that the receptors will share a common ligand but **this rule is not without**

exception (page 371, column 1)). For example the orphanin RQ/nociceptin receptor (has approximately 65% amino acid identity to opioid receptors but does not have high affinity for opioid peptides). Many GPCR subtypes have less than 40% amino acid identity, in which case sequence comparison might not be profitable. Moreover because the ligand-binding pocket has not been described fully for any receptor, it is not feasible to predict ligand identity. There are no signature amino acids that predict either the nature of the ligand or the identity of the interacting Galpha subunit type(s) (page 371). Further, the elusive nature of certain labile natural agonists could be a significant hindrance to the discovery of orphan ligands, as there is no reason to believe that the remaining orphan GPCR ligands will all prove to be peptides. Recently, new complexities have added to the general approach to studying orphan GPCRs. The efficient binding of a ligand to the receptor may require the co-expression of a co-factor protein, e.g. receptor activity modifying protein 1 (RAMP1) in case of amylin binding to orphan GPCR calcitonin receptor-like receptor. Heterodimerization of two subunits may be required for formation of a functional receptor, e.g. GABAb receptor (page 374). The characterization of some GPCR might be more complex than expected, perhaps indicating that functional assays should begin to include co-expression of related orphan GPCRs.

Vanti (Vanti et al., Biochemical and Biophysical Research Communications, Vol. 35, pages 67-71, 2003) discloses the sequence of a receptor does not necessarily provide insights into the nature of its cognate ligand and therefore such receptors are termed orphan GPCRs. Vanti, further

discloses while some GPCRs, e.g. GPR133 and GPR134, may be nearly identical (95%) they are expressed in different CNS tissues suggesting that this family of receptors may have diverse roles in the CNS 9page 70, column 1). Further Vanti discloses the efforts to identify and catalog all human GPCR-encoding genes are ongoing, and these efforts have resulted in the identification of entirely novel signaling systems such as apelin, melanin-concentrating hormone, metastin and urotensin (page 70, column). Based on Vanti's observation it is highly possible that the claimed GPCR may signal through a novel signaling system. The claimed receptor, based on the preceding references could also have a novel natural ligand, that as of yet, has not been identified or purified.

Therefore, references discussed above disclose the unpredictability of assigning a function to a particular protein based on homology, especially one that belongs to the family of GPCRs, which have very different ligand specificity and functions. The discovery of the endogenous ligands will help determine the precise physiological role for each orphan GPCR. As the functions of these novel receptors are uncovered, they could become targets for the development of new pharmacological therapies for diseases not previously considered amenable to pharmacological therapy, but this requires further research and therefore the invention is not complete.

It can be argued the GPCR of SEQ ID NO:20 is useful tool as a reagent or a molecular target in the diagnosis and treatment of GPCR mediated disorders. All members of the GPCR protein family have a utility in selectively screening of

candidate drugs that target GPCRs. However, for a utility to be well established it must be specific, substantial and credible. In this case, as all receptors are in some combination useful in selectively screening of candidate drugs that target GPCRs and in toxicology testing. However, the particulars of screening of candidate drugs, that target GPCR of SEQ ID NO:20, and in toxicology testing are not disclosed in the instant specification. Neither the candidate drugs or toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility, which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to GPCR of SEQ ID NO:20. Because of this, such a utility is not specific and does not constitute a well-established utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed protein for screening compounds that are a target for GPCR of SEQ ID NO:20 is only useful in the sense that the information that is gained from the assay and is dependent on the effect it has on the protein, and says nothing with regard to each individual member of the GPCR family. Again, this is a utility, which would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicants individual GPCR is affected by a test compound in an assay for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed method of using claimed GPCR has no well-established use. The

artisan is required to perform further experimentation on the claimed GPCR itself in order to determine to what use any information regarding this protein could be put.

With regard to diagnosis of disease, in order for a protein to be useful, as asserted, for diagnosis of a disease, there must be a well established or disclosed correlation or relationship between the GPCR of SEQ ID NO:20 and a disease or disorder. The presence of GPCR of SEQ ID NO:20 in tissue is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed GPCR and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the GPCR of SEQ ID NO:20 to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the GPCR of SEQ ID NO:20 is either present only in, e.g. cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of the GPCR of SEQ ID NO:20 as a diagnostic for a disease. However, in the absence of any disclosed relationship between the GPCR of SEQ ID NO:20 and any disease or disorder and the lack of any correlation between the claimed GPCR with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. Congress

intended that no patent be granted on a chemical compound whose sole utility consists of its potential role as an object of use testing. *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

Further, GPCR of SEQ ID NO:20 belongs is a family in which the members have divergent functions based on which tissues the protein is expressed or administered to. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family. The diversity of the GPCRs has already been described. Without some common biological activity for the family members, a new member would not have a specific or substantial utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different biological activities, which may be related to tissue distribution, but there is no evidence that the claimed compounds share any one of diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for drug screening, toxicology testing and diagnosis, is to argue a general, nonspecific utility that would apply to

virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use.

Without knowing a biological significance of the claimed GPCR, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a credible real world manner based on the diversity of biological activities possessed by the GPCR family. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The assertion that the claimed invention has utility in drug screening, drug development and disease diagnosis, do not meet the standards for a specific, substantial or well-established utility for reasons set forth above. None of the utilities identified have been demonstrated to be specific to the polypeptide of SEQ ID NO:20 . One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of the polypeptide SEQ ID NO:20. Applicant has failed with respect to GPCR of SEQ ID NO:20, has not described the family of GPCRs in enough detail to show, by a preponderance of the evidence, that the polypeptide of SEQ ID NO:20 has any substantial use. The record shows that the family of proteins having GPCR domains is diverse, and has such a broad definition, that a common utility cannot be defined. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner,* the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed isolated compounds have any utility.

For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to use the invention.

The use of the claimed invention for toxicology testing, drug discovery, and disease diagnosis are not substantial utilities. The question at issue is

whether or not the broad general assertion that the GPCR of SEQ ID NO:20 might be used for some diagnostic application in the absence of a disclosure of which diagnostic application would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the disclosure satisfies none of the three criteria *See In re Kirk*, 153 USPQ 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.)

The prior rejection under 101 followed *Brenner v. Manson*. In that case, the absence of a demonstrated specific utility for the claimed steroid compound was not ameliorated by the existence of a demonstrated general utility for the class. Unlike *Fujikawa v. Wattanasin*, where there were pharmaceutically acceptable in vitro results, here, there is nothing other than relatively low levels of sequence homology to a broad and diverse family of proteins having distinct modes of activity, and no disclosed common mode of action. A rejection under 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153

USPQ 48 (CCPA 1967). Further since the claimed GPCR has no utility, methods of its use are also rejected for lack of utility.

10. Claims 1-6, 15, 18-21 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the GPCR polypeptide of SEQ ID NO:20 or its encoding polynucleotide (SEQ ID NO:25), further experimentation is necessary to attribute a utility to the claimed GPCR and methods of using said receptor.

The claims fail to disclose how to use the claimed invention for the reasons given above (lack of utility). Further the claims are drawn to an orphan GPCR whose activity, associated G-protein and activating ligands have not been disclosed. Neither the claims nor the specification disclose what specific biological activity is associated with the GPCR of SEQ ID NO:20. There is no disclosure of the specific compounds that are activated in the signal transduction pathway or what ligand is capable of binding to the GPCR of SEQ ID NO:20, so as to disclose a specific function for said GPCR. There is no disclosure of how to assay activity since the natural ligand and function of GPCR of SEQ ID NO:20 is unknown.

The complex nature of GPCRs and the unpredictability of assigning a function to a receptor with no known ligand is described in the rejection under 35 USC 101 and 35 USC 112, 1st paragraph, (also see the teachings of the references cited above, Murdoch, Watson, Kenakin, Karp, Bork, Vanti, Civelli, Hancock, Feng, Marchese and Ta-Tung).

Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation. Further for an agent to be a candidate therapeutic agent, the dysfunction associated with the GPCR of SEQ ID NO:20 must be known. In instant case it is not known what dysfunction is associated with the GPCR of SEQ ID NO:20. The question is even if an agent does bind to with the GPCR of SEQ ID NO:20 or regulates its expression, then what? Applicant still has to find a therapeutic use of said agent. The activity regulated by the GPCR of SEQ ID NO:20 is unknown.

11. If Applicant overcomes the 35 U.S.C. 101 and 112, first paragraph rejections above claims 1c, 1d, and their dependent claims 2-6, 15 and 18-21 would be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims are directed to: a) isolated DNA encoding a protein

comprising the amino acid sequence of SEQ ID NO:20 in which 10% or less of the entire amino acids are substituted, deleted, added, and or inserted, b) an isolated DNA hybridizing under stringent conditions to the DNA comprising the nucleotide sequence of SEQ ID NO:25, c) partial peptide comprising an amino acid sequence of SEQ ID NO:20, d) vector comprising said DNA, transformant comprising said DNA, e)peptide encoded by said DNA, f) method of producing said protein or peptide, g) polynucleotide at least 15 nucleotides of SEQ ID NO:25.

The claimed compounds are directed to variants comprising portions of the GPRv71 polypeptide or polynucleotide. The GPRv71 receptor has no disclosed function, activity or associated ligand. The claims encompass variants with no disclosed activity. Applicant has not disclosed how to use said variants. The claims encompass non-functional variants. Applicant has not disclosed how to use said non-functional variants. As disclosed by Murdoch, Watson, Kenakin, Karp, Bork, Vanti, Civelli, Hancock, Feng, Marchese, Ta-Tung the activity of an orphan GPCRs cannot be reliably predicted from sequence homology to other receptors or pattern of tissue expression. Further the mutation of a single amino acid can render a GPCR inactive or change its activity. The specification does not disclose the critical feature of the invention as it relates structure to function. Nor is there a disclosure of which residue to substitute, delete, add or insert that would produce a functional GPCR. The 10% of the residues of SEQ ID NO:20 that can be substituted, deleted, added or inserted encompasses billions of possible compounds (see written description for calculation). There is no assay

for functionality of the compounds produced. Also there is no disclosure on how to assay DNA that would hybridize to polynucleotide of SEQ ID NO:25 and encode a functional GPCR. The activity of the GPRv71 receptor is unknown. Further polynucleotides comprising 15 nucleotides to the polynucleotide of SEQ ID NO:25 encompass unrelated and inactive variants. Applicant has not disclosed how to use unrelated and inactive variants. Applicant has not disclosed how to isolate or make functional variants encompassing the limitations of the claimed invention.

Pertaining to claim 1d instant fact pattern closely resembles that in Ex parte Maizel, 27 USPQ2d 1662 (BPAI 1992). In Ex parte Maizel, the claimed invention was directed to compounds, which were defined in terms of function rather than sequence (i.e., "biologically functional equivalents"). The disclosed compound in both the instant case and in Ex parte Maizel was the full length, naturally occurring protein. The claimed compound in instant application is a n isolated DNA that hybridizes to the polynucleotide comprising the polynucleotide sequence of SEQ ID NO:25. The critical feature of the invention as it relates structure to function is not required to be contained the hybridizing sequence. In Ex parte Maizel the Board found that there was no reasonable correlation between the scope of exclusive right desired by Appellant and the scope of enablement set forth in the patent application. Even though Appellant in Ex parte Maizel urged that the biologically functional equivalents would consist of proteins having amino acid substitutions wherein the substituted amino acids have similar hydrophobicity and charge characteristics such that the substitutions are

"conservative" and do not modify the basic functional equivalents of the protein, the Board found that the specification did not support such a definition, and that the claims encompassed an unduly broad number of compounds. Such is the instant situation. Clearly, a single disclosed sequence does not support claims to any nucleic acid isolated by the hybridization method using unspecified hybridization conditions, given the lack of guidance regarding what sequences would hybridize specifically to sequence complementary to the polynucleotide of SEQ ID NO:25 and not other, unrelated sequences. Further, many of the polypeptides encoded by the nucleic acids isolated will be unrelated to the protein of SEQ ID No:20, being devoid of its characteristic structural and functional features. The specification does not disclose how to use the unrelated compounds isolated by claimed method. Further, many compounds isolated may be inactive. The specification does not disclose how to use inactive compounds. Inactive compounds may be truncated polynucleotides devoid of function and lacking the critical feature that relates structure to function. Due to the large quantity of experimentation necessary to identify the polypeptides with the structural and functional features of instant invention, the lack of direction/guidance presented in the specification regarding the identification, purification, isolation and characterization of said polynucleotides and polypeptides, the unpredictability of the effects of mutation on the structure and function of proteins and nucleic acids (since mutations of SEQ ID NO:25 and 20 are also encompassed by the claim), and the breadth of the claim which fail to recite meaningful structural and functional limitations, undue experimentation

would be required of the skilled artisan to make or use the claimed invention in its full scope.

As is evidence in the discussions *supra*, undue experimentation would be required by the skilled artisan to make and use the instant invention. Further since the claimed GPCR nucleic acid and protein has no utility, vector comprising the claimed nucleic acid, cell comprising said vector, and method of using said nucleic acid are also rejected under 35 USC 112, 1st paragraph.

Claim Rejection 35 USC 112, 1st paragraph (Written Description)

12. Claims 1-6 and 15, 18-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-6, 15 and 18-21 are directed to: a) isolated DNA encoding a protein comprising the amino acid sequence of SEQ ID NO:20 in which 10% or less of the entire amino acids are substituted, deleted, added, and or inserted, b) an isolated DNA hybridizing under stringent conditions to the DNA comprising the nucleotide sequence of SEQ ID NO:25, c) partial peptide comprising an amino acid sequence of SEQ ID NO:20, d) vector comprising said DNA, transformant comprising said DNA, e)peptide encoded by said DNA, f) method of producing

said protein or peptide, g) polynucleotide at least 15 nucleotides of SEQ ID NO:25.

The claims encompasses polynucleotide that encode polypeptide variants of GPRv71 GPCR with no disclosed activity or function. The ability to hybridize to a sequence does not disclose the critical feature of the invention that is required for activity for GPRv71. The mutated variants do not require that the structure required for activity be contained in the variants. The partial peptides not the partial polynucleotides any structure to be retained that is required for functionality. The functionality (activity) of the GPRv71 is neither claimed nor known (see previous utility rejection)

Therefore nucleic acid molecules encoding variants of the protein disclosed in SEQ ID NO:20, said variants may be completely unrelated, structurally and functionally to the protein encoded by the polynucleotide of SEQ ID NO:25 are encompassed by the claims. The common function of the nucleic acid (SEQ ID NO:25) encoding the polypeptide (SEQ ID NO:20), which is based upon a common property or critical technical feature of the genus claimed is not disclosed. The ligand that binds GPRv71 is not disclosed. The claims, as written, encompass nucleic acid encoding polypeptides which vary substantially in length and also in amino acid composition. The instant disclosure of a polynucleotide of SEQ ID NO:25 encoding the polypeptide of SEQ ID NO:20 does not adequately describe the scope of the use of the claimed genus, which encompasses a substantial variety of subgenera including polynucleotides, variants of said polynucleotides, allelic variants, chimeric constructs, fusion

constructs which may encode polypeptides completely, unrelated functionally to the polypeptide of SEQ ID NO:20. A description of a genus of polypeptides or polynucleotides may be achieved by means of a recitation of a representative number of polypeptides, defined by amino acid sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Instant specification fails to provide sufficient descriptive information, such as definitive structural and functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. For example, what regions and fragments of the claimed GPCR contain a definitive structural feature required for protein function? The specification proposes to discover other members of the genus by using screening assays and techniques involving probes, primers, and hybridization. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and proteins encompassed. No identifying characteristic or property of the instant polypeptides/polynucleotide is provided such that one of skill would be able to predictably identify the encompassed

molecules as being identical to those instantly claimed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific polypeptide and nucleotide sequences and the inability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe, enable and use the genus as broadly claimed. The skilled artisan cannot envision the detailed chemical structure of the encompassed proteins and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. It is acknowledged that the skill of the artisan in the molecular biology art is high. However, in the current instance, there is no clear evidence of the specific activity possessed by the claimed genus of nucleic acid molecules encoding variant GPRv71 polypeptides, the critical special technical feature of the polypeptides or how the critical special technical feature encompassed by the genus claimed relates to function. Because of the lack of guidance in the prior art and current application, one skilled in the art could not predict if the variants GPRv71 have the same activity as the protein disclosed in SEQ ID NO:20, since no activity is disclosed, or if they contain the domain(s) of SEQ ID NO:20, containing the critical special technical feature of the claimed GPRv71, since no critical special

technical feature is disclosed. The specification discloses GPRv71 is an orphan receptor, i.e. receptor with no known ligand and function.

The skilled artisan cannot envision the detailed chemical structure of the encompassed compounds and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115). Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid or polypeptide is itself is required. See *Fibers v. Revel*, 25 USPQ d. 1601 at 1606 (CAFC 1993) and *Amen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a

genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". Therefore the specification fails to disclose the activity of the claimed genus of polypeptides/polynucleotides, the critical special technical feature of the polypeptides/polynucleotides or how the critical special technical feature encompassed by the fragments and variants of claimed GPRv71 relates to function.

The claims encompass nucleic acids encoding proteins which are structurally and functionally unrelated to the protein/nucleic acid disclosed in SEQ ID NO:20 and 25, respectively. Therefore instant specification fails to provide sufficient descriptive information, such as definitive structural/ functional features of the claimed genus of nucleic acids/polypeptides . There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no disclosure of the specific activity of claimed GPRv71 and how it is specifically assayed. The specification nor claims disclose the specific activity of the GPRv71 of instant invention nor a description of the conserved regions which are critical to the structure and function of the genus claimed.

The claimed nucleic acid encodes an orphan receptor GPRv71 whose activity, associated function and activating ligands have not been disclosed. The neither specification nor prior art provide a specific assay for the genus claimed. The superfamily of GPCRs is specialized proteins designed for chemical recognition of specific ligands and subsequent transduction of information encoded in those ligands/compounds to the machinery of the cell. GPCRs interact with many diverse compounds having diverse effects. The important features which would help to define the GPRv71 activity and define the genus claimed have not been disclosed in the specification nor prior art. Further the activity transduced is not disclosed or how it relates structure to function.

Therefore instant specification fails to provide sufficient descriptive information, such as definitive structural/ functional features of the claimed genus of polypeptides/polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. The neither specification nor claims disclose the specific activity of the orphan GPRv71 of instant invention, how it is assayed, nor a description of the conserved regions which are critical to the structure and function of the genus claimed. Further vector comprising the claimed nucleic acid, transformant comprising said vector are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the polypeptide has been isolated. Thus, claiming all polypeptides that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. The claims recite a broad arbitrary structural relationship between the claimed polypeptide sequences. The claims are not even directed to functional protein. Therefore non-functional or functionally unrelated proteins to GPRv71 are encompassed by the claims. The recited structural relationships are arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level; and the specification does not describe a single species of nucleic acid that encodes a functional protein that is not either 100% identical to the recited nucleotide sequence or that encodes a polypeptide that is not 100% identical to the recited amino acid sequence.

While one of skill in the art can readily envision numerable species of nucleic acid sequences that are at least a given % identity to a reference nucleotide sequence and that encode a polypeptide at least a given % identity to a recited reference amino acid sequence, one cannot envision which of these

also encode a polypeptide with a specific activity of the protein of SEQ ID NO:20. The fact remains that the actual nucleic acid sequences which encode a protein with a particular activity or the actual amino acid sequences of such a protein *cannot* be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with an arbitrary structural relationship with a known functional sequence. For example, if one skilled in the art were to make a synthetic nucleotide sequence that encoded a polypeptide with 90% identity to the reference amino acid sequence, he would be no more able to say whether it encoded a functional polypeptide than if the nucleotide sequence encoded a polypeptide that was only 10% identical to the reference polypeptide sequence. Nor would he be able to say whether the sequence existed in nature.

To put the situation in perspective, the number of possible amino acid sequences of 100 amino acids in length is 20^{100} (approx. 10^{130}) and the number of possible nucleotide sequences of 300 nucleotides in length is 4^{300} (approx. 4×10^{180}) . The number of possible nucleotide or amino acid sequences that are of a given %identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + \ldots + X^{n-1}L(L-1)(L-2)\ldots(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)\ldots(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the

length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids).

For a 100 amino acid sequence that is at least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6×10^{23}. Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1×10^{26}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula $X^nL^n/n!$, where $n<<L$. Using this formula to approximate N in this example gives a value of 1.7×10^{26}. For a 300-nucleotide reference sequence, the number of possible 300 nucleotide sequences that are at least 90% identical to the reference is approximately 1.6×10^{56}.

In the present case, the reference amino acid sequence, SEQ ID NO:25, is 508 amino acids long, and the reference nucleotide sequence, SEQ ID NO:20 is 1002 nucleotides long. Using the approximation formula, the number of possible amino acid sequences and nucleotide sequences that are at least e.g. 90% identical to the reference amino acid sequence or nucleotide sequence, would be much larger than 6×10^{23} and 1.6×10^{56}, respectively. While limiting the scope of potential sequences to those that are at least e.g. 90% identical or

comprising 15 nucleotides or a partial peptide to a reference greatly reduces the number of potential sequences to test, it does not do so in any meaningful way. Thus, limiting the claims by the recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those which encode a functional protein encompassed by the claims. Therefore, inclusion of the structural relationships in the claim does not distinguish the instant fact situation from those reviewed in *Amgen, Fiers,* and *Regents of the Univ. Calif.*

The specification does not provide any information on what amino acid residues are necessary and sufficient for a functional activity. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in an active GPRv71polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there are no other examples of proteins that have structural homology with SEQ ID NO:20 that would be predictive of the activity of claimed GPCR. It is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. Therefore one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in case-to-case painstaking experimental study to determine active GPRv71 variants. Consequently, excessive trial and error experimentation would have been required to identify the necessary nucleic acid sequence derivatives encoding a biologically active GPRv71 with an amino

acid sequence differing from SEQ ID NO:20 since the amino acid sequence of such polypeptides could not be predicted.

The specification discloses only one putative amino acid sequences, SEQ ID NO:20, for a polypeptide having the necessary properties for the disclosed uses, and provides no guidance on obtaining functional polypeptide variants of SEQ ID NO:20 encoded by SEQ ID NO:25 which would be suitable.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 , clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing daté sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird,* 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF'S were

found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polynucleotides encoding polypeptides comprising the amino acid sequence set forth in SEQ ID NO:20 but not the full breadth of the claims meets the written description provision of 35 U.S.C.112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1 115).

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 15, 18-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Boucher et al (US Patent 5596088).

Boucher discloses a polynucleotide which has 20.5% identity and 56.4% best local similarity to the GPCR of SEQ ID NO:20 of instant application. The polynucleotide of Boucher would hybridize to the polynucleotide of SEQ ID No:, comprises at least 15 nucleotides of SEQ ID NO:25, encodes an isolated DNA

encoding a protein comprising **an** amino acid sequence of SEQ ID NO:20, and encodes a partial peptide of a protein comprising **an** amino acid sequence of SEQ ID NO:20. Boucher further discloses vector comprising said DNA, transformant comprising the DNA and peptide encoded by said DNA, thereby meeting the limitations of claims 1-6, 15, 18-21, absent evidence to the contrary. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nirmal S. Basi
Art Unit 1646
April3, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER